A Phase II Trial of Salirasib in Patients with Lung Adenocarcinomas with *KRAS* Mutations

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Introduction: *KRAS* mutations are present in 30% of lung adenocarcinomas. Salirasib prevents Ras membrane binding thereby blocking the function of all Ras isoforms. This phase II study determined the activity of salirasib in patients with advanced lung adenocarcinomas with *KRAS* mutations.

Methods: Two cohorts of patients with stage IIIB/IV lung adenocarcinoma were eligible: patients with tumors with *KRAS* mutations who were previously treated with chemotherapy and patients receiving initial therapy who had ≥15 pack-year smoking history. Salirasib was given orally from days 1 to 28 of a 35-day cycle. The primary end point was the rate of nonprogression at 10 weeks.

Results: Thirty-three patients were enrolled. Thirty patients had *KRAS* mutations (23 patients who were previously treated and 7/10 patients who had no prior therapy). Of the previously treated patients, 7 of 23 (30%) had stable disease at 10 weeks, and 4 of 10 (40%) previously untreated patients had stable disease at 10 weeks. No patient had a radiographic partial response (0% observed rate, 95% confidence interval 0–12%). The median overall survival was not reached (>9 months) for previously untreated patients and it was 15 months for patients who received prior chemotherapy. Diarrhea, nausea, and fatigue were the most common toxicities.

Conclusions: Salirasib at the current dose and schedule has insufficient activity in the treatment of *KRAS* mutant lung adenocarcinoma to warrant further evaluation. The successful enrollment of 30 patients with tumors with *KRAS* mutant lung adenocarcinoma over 15 months at a single site demonstrates that drug trials directed at a *KRAS*-specific genotype in lung cancer are feasible.

Key Words: Lung adenocarcinoma, Salirasib, KRAS.

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KRAS is an oncogene that is mutated in approximately 30% of lung adenocarcinomas diagnosed in the United States. This oncogene encodes one of three isoforms of Ras (N-Ras, K-Ras, and H-Ras) which, when mutated, lead to tumor formation. Somatic *KRAS* mutations in non-small cell lung cancer (NSCLC) were identified more than 25 years ago.[1] *KRAS* mutations are more common in lung adenocarcinomas from patients with a heavy cigarette smoking history, but they also occur in patients who never smoked cigarettes.[2] *KRAS* mutations predict absence of response to gefitinib and erlotinib in lung cancer.[3] The value of *KRAS* mutations as a predictive and prognostic factor in NSCLC has not been thoroughly evaluated in the context of other known risk factors.[4]

Ras signaling leads to activation of effector pathways which causes cellular proliferation, survival, and alteration of gene expression (reviewed in Ref. [5]). Point mutations in Ras lead to loss of GTPase activity resulting in constitutive signaling. In animal models, expression of mutant *KRAS* leads to tumor formation.[6,7] In such models, continued expression of mutant *KRAS* is necessary for tumor maintenance as evidenced by apoptosis and tumor regression when mutant *KRAS* is no longer expressed. This requirement for continued Ras activation for tumor maintenance makes it a target for anticancer drugs.

Salirasib (s-trans, *trans*-farnesylthiosalicylic acid) decreases the activity of activated Ras by competitively inhibiting the attachment of GTP-bound Ras to the plasma membrane.[8] By preventing membrane binding, Ras signaling is blocked. Salirasib inhibits all isoforms of Ras in contrast to farnesyltransferase inhibitors, which fail to inhibit K-Ras and N-Ras function due to alternative membrane-binding mechanisms.[9] Salirasib has been shown to reduce tumor growth and

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total cell K-Ras levels in A549, H1299, and HTB54 as both a single agent and in combination with chemotherapy.[10,11]

In a phase I trial, salirasib dosing was evaluated in patients with advanced cancers and neurofibromatosis.[12] The most commonly observed toxicities were diarrhea (grades 1–2, present in 79% of patients), fatigue, nausea, and vomiting. In the absence of grade 3 or 4 dose-limiting toxicities, dose escalation was discontinued at 800 mg twice daily (on days 1–21 of a 28-day cycle) because of persistent grades 1 to 2 diarrhea, making this the maximum tolerated dose. No patients with lung cancer were treated in the phase I trial.

We hypothesized that salirasib would prevent tumor growth or lead to tumor shrinkage in patients with *KRAS* mutant lung adenocarcinoma. We conducted this phase II trial to assess the efficacy of single-agent salirasib as the initial treatment of lung adenocarcinoma and in patients with *KRAS* mutations who had been previously treated with chemotherapy. Patients with previously untreated lung adenocarcinoma were limited to those patients with a smoking history of ≥15 pack-years to reduce the frequency of patients with epidermal growth factor receptor mutations in this cohort.[13]

PATIENTS AND METHODS

Eligibility

Patients with stage IIIB or IV lung adenocarcinoma with measurable disease by RECIST were candidates for this trial. Two groups of patients were eligible: previously untreated patients with lung adenocarcinoma with a smoking history of ≥15 pack-years (previously untreated) or those with a documented *KRAS* mutation and any number of prior therapies (previously treated). Other eligibility criteria included age 18 years or older, Karnofsky Performance Status of 70% or greater, and adequate renal and hepatic function. Patients with symptomatic or progressing central nervous system metastases or who had received chemotherapy or radiotherapy in the 3 weeks before starting therapy were excluded. The clinical trial protocol and informed consent were approved by the Memorial Sloan-Kettering Cancer Center Institutional Review Board. All patients provided written informed consent.

Study Evaluations and Drug Administration

A medical history, physical examination, complete blood count, and comprehensive metabolic panel were measured within 2 weeks before study entry and at initiation of each cycle of therapy (every 5 weeks). Patients were assessed for toxicity based on National Cancer Institute Common Toxicity Criteria for Adverse events, version 3.0. Objective tumor responses were determined by imaging of all known sites of disease less than 4 weeks before study entry, after 4 and 10 weeks of treatment, and then every 10 weeks thereafter using RECIST 1.0.

Patients were treated with salirasib 800 mg twice daily on days 1 to 28 of a 35-day cycle. The schedule of days 1 to 28 of a 35-day cycle was chosen to allow initial imaging after 4 weeks of continual treatment. After 10 patients were enrolled, because of toxicity (described in Results), the initial dose was changed to 600 mg twice daily.

Statistical Analysis

The primary end point was the rate of nonprogression (RECIST complete response + partial response + stable disease) at 10 weeks for patients treated with salirasib. Secondary end points included RECIST response rate, duration of response, time to disease progression, and overall survival for patients treated with salirasib. Sample size was determined for two groups of patients (patients previously treated with known *KRAS* mutation and patients previously untreated). For patients who had been previously treated, a Simon two-stage minmax design was chosen with an $\alpha = 0.05$, $\beta = 0.2$ with a null 10-week stable disease rate of 20%, and an alternative stable disease rate of 40%. For this design, initially 18 patients were to be enrolled and, if 5 or more patients had 10-week stable disease, an additional 15 patients were to be enrolled. For previously untreated patients, a Simon two-stage minmax design was chosen with an $\alpha = 0.05$ and $\beta = 0.1$ for a null 10-week stable disease rate of 5% and an alternative 10-week stable disease rate of 20%. A lower alternative hypothesis response rate was chosen for this group because *KRAS* mutation was not required for enrollment. For this design, 29 patients were to be enrolled in stage I. If one patient had stable disease at 10 weeks, then an additional nine patients were to be enrolled. Although there were no additional predefined stopping points for efficacy analysis, in the absence of any radiographic partial responses, further enrollment was discontinued after a total of 33 patients were enrolled.

RESULTS

Between August 2007 and December 2008, 33 patients were enrolled and treated with salirasib. Baseline characteristics are listed in Table 1.

Efficacy

Of previously treated patients, 7 of 23 (30%, 95% confidence interval: 15–51%) had stable disease at 10 weeks and 4 of 10 (40%, 95% confidence interval: 17–69%) previously untreated patients had stable disease at 10 weeks. Of

TABLE 1. Baseline Characteristics

Characteristic	Total ($n = 33$)	Previously Untreated ($n = 10$)	Previously Treated ($n = 23$)
Median age (range), yr	68 (46–82)	73 (64–79)	65 (46–82)
Sex			
Female	20	7	13
Male	13	3	10
KRAS mutation			
Yes	30	7	23
No	2	2	0
Unknown	1	1	0
Smoking history			
Never	3	0	3
Former (<15 pack-years)	4	0	4
Former (≥15 pack-years)	26	10	16
Prior lines of therapy, median (range)	1 (1–8)	0	2 (1–8)

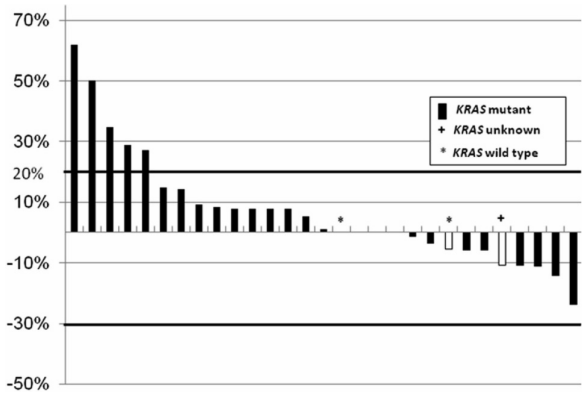

FIGURE 1. Best response for indicator lesions (RECIST) for individual patients.

TABLE 2. Toxicities During Salirasib Treatment

	Grade 1	Grade 2	Grade 3	Grade 4	Total
Diarrhea	20	4	5	0	29
Nausea	16	1	1	0	18
Fatigue	9	7	2	0	18
Dyspnea	1	2	4	0	7
Rash	6	0	0	0	6
Cough	2	3	0	0	5
Constipation	4	0	0	0	4
Abdominal pain	3	0	0	0	3
Peripheral edema	3	0	0	0	3
Neuropathy	3	0	0	0	3

the 11 patients with nonprogression at 10 weeks, the median time of stable disease was 7 months (range 5–25 months). No patients had a radiographic partial response (Figure 1). As 30 of 33 patients had documented *KRAS* mutations, association of *KRAS* mutation status and outcomes was not possible. The median time to progression was 2 months for patients previously untreated and 1 month for patients previously treated with chemotherapy. The median overall survival was not reached (>9 months) for previously untreated patients and 15 months for patients who had received prior chemotherapy.

Toxicity

Diarrhea, nausea, and fatigue were the most common toxicities (Table 2). Three patients withdrew due to drug-related diarrhea before completing 10 weeks of therapy. Among the first 10 patients, 2 required a dose reduction because of intolerable grade 2 diarrhea and 2 withdrew from the study with grade 3 diarrhea. The remaining patients enrolled in the study received 600 mg twice daily as the starting dose. In total, 24% of patients had drug-related grade 3 adverse events (five patients with diarrhea, two patients with grade 3 fatigue, and one patient with nausea). Four patients had grade 3 dyspnea on study that was attributed to disease progression. There were no grade 4 or 5 drug-related adverse events.

DISCUSSION

In this study, we report a prospective phase II trial of salirasib in patients with *KRAS* mutant NSCLC. Treatment with salirasib was associated with modest toxicity (mostly diarrhea), and no significant antitumor activity with no partial responses observed. On the basis of these data, salirasib monotherapy at the current dose and schedule (days 1–28 of a 35-day cycle) has insufficient activity in the treatment of *KRAS* mutant lung adenocarcinoma to warrant further evaluation.

To our knowledge, this is the first report of a prospective clinical trial in patients with NSCLC that required documented *KRAS* mutation for inclusion. This clinical trial accrued in a relatively short period of time (accruing 30 patients with *KRAS* mutant lung adenocarcinoma at a single site in 15 months), demonstrating the feasibility of this genotype-specific approach for evaluation of therapies for patients with lung adenocarcinoma with *KRAS* mutations.

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